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DRAWINGS ATTACHED

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(54) LAYERED BOLUS FOR ANIMAL HUSBANDRY PROVIDING FOR IMMEDIATE AND SUSTAINED RELEASE OF MEDICAMENT

(71) We, SMITH KLINE & FRENCH LABORATORIES, of 1500 Spring Garden Street, City of Philadelphia, Commonwealth of Pennsylvania, 19101, United States of America, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a dosage form to be employed in veterinary practice, particularly for the administration of therapeutic substances to ruminants such as cattle and sheep. More specifically, this invention relates to a layered bolus which provides both a rapid and sustained release of a therapeutically active substance in a single unit dose.

The sustained release bolus employed for veterinary practice is known to the patent art. These dosage forms have sufficient dimensions as to density and weight to stop in the rumeno-reticular sac and remain there rather than pass into the alimentary tract and be eliminated intact. The physical form of these dosage units is retained over a long period of time in the sac while the therapeutically active substance is slowly released by erosive or solubilization action within the rumeno-reticular sac. In other words, regardless of the therapeutically active substance to be administered, the bolus itself must comply with the physical requirements as to density and weight. In order to meet the proper requirements for density and weight, iron or any other relatively high density matrix may be employed in the preparation of the bolus. Specification No. 866924 discloses a veterinary bolus which provides for the biologically active substance over an extended period of time. In the case of a therapeutic substance such as, for example, a sulfonamide or an antibiotic, the patent reveals it would be possible to provide a blood level of three months or more. The above noted patent also discloses that the rate of release is accomplished by varying the firing temperature used in the preparation of the pellets. Extremely high temperatures are employed to heat pellets intended to remain in the rumeno-reticular sac of animals for a prolonged period of time. The prolonged medication provided by the process of Specification No. 866924 can last from weeks to in excess of a year and is desired in order to prevent retardation of growth and development of the animal, i.e., more of a prophylactic type of medication than curative.

Instead of having the medication remain for months or a year as taught by the above noted patent, it is often necessary to dose a sick animal several weeks before slaughtering with a sulfonamide or other such medicament. When dealing with food producing ruminants, any medication given in therapeutic doses should be essentially clear of the tissues before the animals are slaughtered. United States Patent No. 3,507,952 discloses an improved sustained release bolus for veterinary use which meets the above release requirement. The patent reveals a bolus having a predictable and controlled sustained release pattern of the medicament over a relatively short period, i.e., the bolus disintegrates in the rumen in about ten days and the animal tissues are clear of the medicament in three weeks.

However, there is still one major problem which these prior art boluses fail to solve. It takes at least twelve hours post administration for any of the known sustained release sulfonamide boluses to show therapeutic plasma levels. The recommended minimal therapeutic sulfonamide level is 5 mg./100 ml. when administering these long acting sulfonamides to ruminants, additional intravenous or regular sulfonamide tablets must also be administered to provide an initial high level. In brief, concurrent treatment of ruminants with either a parenteral or tablet dosage form plus the sus-

tained release bolus is necessary to insure rapid therapeutic blood levels as well as prolonged therapy.

Scours, which is a highly infectious disease in calves the first few days after birth, is a typical example where immediate antibiotic medication is necessary. This disease is caused by microorganisms and due to the acuteness of the illness, it is imperative that medication be made available to the animal from the dosage form as soon as possible. The calf has need for both an immediate medication to eliminate the bacterial invasion and a sustained release effect to treat the diarrhea symptomatically.

It is therefore the object of the present invention to provide a single dosage form which provides for both a rapid therapeutic blood level and prolonged therapy which is essential in antibiotic treatment of ruminants. This dosage form would eliminate the need of a concomitant parenteral dose.

It is a further object of this invention to provide a single dosage form for food producing ruminants which increases the rapidity of obtaining adequate blood levels and decreases post treatment withdrawal time required with prolonged action sulfonamides.

Now in accordance with this invention there is provided a sustained release veterinary layered bolus comprising an immediate release layer and, contiguous therewith, a sustained release layer, said immediate release layer having a disintegration time in the rumen of less than thirty minutes and comprising sufficient of a medicament rapidly to provide a therapeutic level of said medicament in the blood of the ruminant animal to which the bolus is administered and said sustained release layer comprising a filler matrix of such a density that the bolus will lodge in the rumeno-reticular sac of the ruminant animal and sufficient of said medicament that, at the rate of disintegration of said sustained release layer, a therapeutic level of said medicament is maintained in the blood of the ruminant animal to which the bolus is administered for at least 72 hours from the time of dosage.

The layered bolus of this invention provides for plasma levels higher than the recommended minimal therapeutic level (5 mg./%) in less than half the time it requires the prior art bolus to reach this level. The bolus is further advantageous in that it can be administered to food producing ruminants for therapeutic effect several weeks before slaughtering and the medicament present will be essentially clear of the animal tissues at the time of slaughtering, i.e., post treatment withdrawal time is decreased.

The bolus of this invention therefore solves the prior art disadvantage of not being able to obtain both an immediate and sustained release of a medicament in a single dose and fill a commercial need of such a dosage unit in the veterinary field.

Layered tablets for human administration are well known to the pharmaceutical art. However, there is no prior art dislosing a layered bolus of the magnitude and having both immediate and sustained release characteristics noted above as necessary for certain veterinary diseases.

The differences between the prior art layered tablet and sustained release layered bolus of this invention are clearly apparent from the ensuing description taken together with the accompanying drawing wherein:

Figure 1 is a side elevation of the prior art layered tablet;

Figure 2 is a side elevation of a layered bolus of the present invention;

Figure 3 is a top plan view of the layered bolus;

Figure 4 is an end view of the layered bolus shown in Figure 2;

Figure 5 is a transverse sectional view as seen along the line 5—5 of Figure 3.

Referring specifically to Figure 1, layered tablet 2 has an immediate release layer 4 and a sustained release layer 6. This tablet represents one of the largest prior art layered tablets. The tablet weighs approximately 1.0 grams, has a diameter of 0.503 inches and a thickness of 0.22 inches.

In Figures 2 to 5 the sustained release layered bolus of this invention is disclosed. Bolus 10 weighs 25.97 grams and has an immediate release layer 12 and a sustained release layer 14. The length of the bolus taken horizontally along Figure 2 is approximately 2.733 inches. The width of the bolus as measured vertically in Figure 3 is 0.864 inches and the thickness of the bolus as measured vertically in Figure 4 is 0.630 inches.

A further view of immediate release layer 12 and sustained release layer 14 is presented in the cross section as represented in Figure 5.

In brief, the average layered bolus as embraced by this invention and disclosed in Figure 2 weighs 26 times more than the closest prior art layered tablets. Other dimensions such as thickness and length range from 3 to 6 times greater than presently available layered tablets. In order to prepare the layered bolus of this invention, a specially modified tablet machine is necessary.

The method for the preparation of a bolus according to the present invention comprises preparing separate immediate and sustained release granulations containing a medicament and a filler which at least in the sustained release granulation is of such a density that the bolus will lodge in the rumeno-reticular sac of the ruminant animal, placing said granulations in separate hoppers and selectively compressing said granulations into a layered bolus.

The sustained release effect is accomplished by employing in the sustained release layer of our bolus a lubricant in certain critical percentage ranges as detailed in United States Patent No. 3,507,952.

Tablet disintegrants-such as, for example, starch may be used to facilitate disintegration of this layer.

The lubricant employed in the sustained release layer can be any of the more common tablet water insoluble lubricants, such as, for example, magnesium stearate, sodium stearate, calcium stearate, powdered stearic acid, talc, paraffin, cocoa butter, graphite, lycopodium or combinations thereof. The preferred lubricants are fatty acid derivatives especially the stearates, such as, for example, magnesium stearate, sodium stearate, calcium stearate and stearic acid. In order to achieve a definite predictable sustained release pattern, the lubricant material should be present from about 1% to about 3.5% by weight of the sustained release layer. Most advantageously, the lubricant will be present from 2.5% to 3.5% by weight of the sustained release layer.

Exemplary of the dense fillers which may be employed as a matrix are iron powder, calcium sulfate dihydrate, Portland cement, plaster of Paris, magnesium oxyiodide cement or mixtures thereof. The filler will be present from 5% to 95% by weight of the total solids. Preferably the filler will be present from 25% to 75%.

When binders or granulating agents are necessary to insure adequate cohesiveness of the bolus, natural gums and gum constituents such as, for example, acacia, tragacanth, agar, and pectin may be employed. Further, exemplary of binders would be, for example, cellulose esters, polyvinyl-pyrrolidone and proteinaceous material such as, for example, gelatin, casein and zein.

It will be evident to one skilled in the tableting art that the binder is a standard pharmaceutical tool commonly used and is not an essential aspect of this invention, therefore the amount of binder can be varied.

The veterinary layered bolus in accordance with this invention and a method for its preparation will be further illustrated by the following specific example:

EXAMPLE

A granulation is prepared from the following powders:

Sustained Release Granules

Ingredients	*Gms./Bolus*
Sulfamethazine, U.S.P.	13.000
Calcium Sulfate, Dihydrate	7.000
Polyvinylpyrrolidone	1.125
F.D. & C. Yellow #5 Dye	0.005
F.D. & C. Blue #1 Dye	0.005
Purified Water	Variable
Magnesium Stearate	0.213

The polyvinylpyrrolidone, yellow and blue dyes are dissolved in water. The sulfamethazine and calcium sulfate, dihydrate powders are mixed and granulated with the polyvinylpyrrolidone dye solution. The mixture is screened and dried overnight at 120°F. The dried granulation is passed through a No. 8 U.S. Standard screen and the magnesium stearate is added to the granulation with mixing.

Immediate Release Granules

Ingredients	*Gms./Bolus*
Sulfamethazine, U.S.P.	3.0000
Calcium Carbonate, Precipitated, U.S.P.	0.0860
Glycine, N.F.	0.4290
Starch, U.S.P.	0.4290
Polyvinylpyrrolidone (PVP)	0.2150
F.D. & C. Yellow #5 Dye	0.0009
Purified water, U.S.P.	variable
Starch, U.S.P.	0.2574
Alginic Acid	0.2574
Dioctyl Sodium Sulfosuccinate, N.F.	0.0129

The sulfamethazine, calcium carbonate, glycine and starch powders are thoroughly mixed. The mixture is granulated with an aqueous solution of the PVP and yellow dye. The wet mixture is passed through a No. 4 U.S. Standard screen on an oscillating granulator onto drying trays. The screened mixture is then dried at 120°F. for 12 hours. The dried granulation is passed through a No. 8 U.S. Standard screen on the Stokes oscillating granulator and the remainder of the starch is added together with alginic acid and dioctyl sodium sulfosuccinate.

The immediate and sustained release granulations are placed in separate hoppers in a modified Stokes DD2—11HH tableting machine using oblong punches having a size of 0.860″ × 2.725″ and concaved on a 1-3/4″ diameter wheel, 0.110″ deep with a 0.10″ flat edge. The sustained release granules are first fed into the die with the lower punch adjusted at such a depth to give the desired fill weight. The upper punch then tamps the sustained release granules just sufficiently to form a cohesive layer. The die then moves to the second hopper containing the immediate release granules. These granules are fed into the die on top of the sustained release layer wherein both granulations are then fully compressed to the desired hardness.

The final product is a compressed oblong layered bolus comprising a mixture of a therapeutically active substance, an inert dense filler and from 1.0% to 3.5% of a lubricant. The bolus provides for a controlled release pattern providing both an immediate and sustained release of the medicament. The finished bolus will weigh from 10.0 grams to 50.0 grams and have a density up to 8.0. Advantageously the finished bolus will weight from 20.0 grams to

40.0 grams and have a density of 1.5 to 5.0. The length of the bolus will be from 1.5 inches to 3.0 inches. The immediate release layer completely disintegrates within a half hour and rapidly provides a therapeutic blood level of the therapeutically active substance. The sustained release layer disintegrates within 48 hours and provides a controlled sustained release of the medicament maintaining a therapeutic level for at least 72 hours. The medicament is essentially clear of the tissues in approximately two weeks.

The layered boluses of this invention containing sulfamethazine were tested *in vivo* to determine the plasma levels of free sulfonamide in cattle and also to observe drug residues in tissues over a period of time. The experimental subjects for this study were twelve Hereford heifers. Each animal was dosed as close as possible to 220 mg./kg. of body weight. Blood was drawn aseptically from the jugular vein in heparinized vacutainers at 0, 6, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, and 264 hours inclusive after dosing and analyzed for sulfonamide.

Three animals were killed at 48 hours, three at 144 hours, three at 240 hours, and three at 264 hours after administration of boluses and in each case both kidneys and 1.0 kg. of each of the following tissues collected and immediately frozen: skeletal muscle, fat and liver. The frozen tissues were later assayed for the presence of the sulfonamide.

The results of these *in vivo* tests are presented in the following tables. Table 1 represents plasma concentrations of sulfamethazine after administration of the layered bolus.

TABLE 1

Mg. Sulfamethazine per 100 ml. Plasma

Animal No.	Time (Hours)								
	0	6	12	24	48	72	96	120	144
254	0.00	7.53	10.57	15.58	13.17	6.73	1.72	0.24	0.10
255	0.00	6.02	9.63	12.89	9.80	—	—	—	—
256	0.00	5.49	6.94	6.88	8.44	7.97	4.65	1.50	0.35
258	0.00	6.73	9.38	12.92	11.58	5.95	1.92	0.35	0.11
259	0.00	6.24	8.74	11.73	10.80	3.78	0.72	0.11	0.00
260	0.00	6.14	8.98	9.41	8.44	—	—	—	—
261	0.00	5.66	9.29	14.28	10.87	8.22	2.98	0.36	0.11
263	0.00	5.40	7.56	7.94	7.49	5.42	2.74	0.51	0.11
264	0.00	4.85	7.84	13.21	11.53	4.87	1.05	0.12	0.00
265	0.00	4.83	5.65	6.60	10.50	8.13	2.87	0.51	0.25
267	0.00	5.99	7.71	8.55	5.81	—	—	—	—
268	0.00	7.08	10.66	12.81	7.54	2.35	0.61	0.11	0.00
MEAN	0.00	6.00	8.61	11.07	9.66	5.94	2.14	0.42	0.11

TABLE 2

Free Sulfonamidide Tissue Levels

Time of Tissue Harvest	PPM Free Sulfonamide			
	Fat	Muscle	Kidney	Liver
48 hr.	6.30	17.33	15.70	20.50
144 hr.	0.10	<0.20	0.52	0.62
240 hr.	<0.04	<0.04	<0.04	<0.04
264 hr.	<0.04	<0.04	<0.04	<0.04

The above results indicate that mean levels of 6.0 mg./100 ml. were present in six hours with 5.94 mg./100 ml. still remaining after 72 hours. Both of these levels are above the recommended minimal therapeutic level of 5 mg./100 ml. The animal tissues showed residues of less than 0.04 ppm sulfonamide ten days after administration.

In summary, the above standard animal test procedure demonstrates that when a layered sustained release bolus according to this invention is administered to cattle therapeutic blood levels were rapidly achieved and maintained for days. Further the withdrawal time of the medicament from the tissues has been decreased. The reported tissue residues require a 21 day withdrawal before meat from treated animals may be used for human consumption. As noted above, the sulfamethazine was relatively clear of the tissues ten days post administration.

Although the invention is specifically exemplified using sulfamethazine since the advantages are particularly suited to this medication, it will be appreciated that it is useful with any solid medicament which it is desired to provide in combined immediate and sustained release form. The medicament may be in the form of a base, salt or ester and may be soluble or insoluble in nature. Thus, for example, the medicament may be a sulfonamide derivative such as sulfamethazine, sulfathiazine, a tranquilizer such as chlorpromazine, an antibiotic such as chloramphenicol, tetracycline or penicillin, an anthelmintic such as piperazine phosphate, an anti-bloat agent such as organopolysiloxane, hormone growth supplements such as stilbesterol and many more medicaments such as vitamins and those used in the treatment of bacterial enteritis such as furazolidone.

WHAT WE CLAIM IS:—

1. A sustained release veterinary layered bolus comprising an immediate release layer and contiguous therewith, a sustained release layer, said immediate release layer having a disintegration time in the rumen of less than thirty minutes and comprising sufficient of a medicament rapidly to provide a therapeutic level of said medicament in the blood of the ruminant animal to which the bolus is administered and said sustained release layer comprising a filler matrix of such a density that the bolus will lodge in the rumeno-reticular sac of the ruminant animal and sufficient of said medicament that, at the rate of disintegration of said sustained release layer, a therapeutic level of said medicament is maintained in the blood of the ruminant animal to which the bolus is administered for at least 72 hours from the time of dosage.

2. A veterinary bolus according to claim 1 wherein the medicament is a sulfonamide or antibiotic and the filler matrix is calcium sulfate dihydrate or iron powder.

3. A veterinary bolus according to claim 2 wherein the medicament is sulfamethazine and the filled matrix is calcium sulphate dihydrate.

4. A veterinary bolus according to claim 1 as hereinbefore described and as illustrated in Figures 2 to 5 of the accompanying drawings.

5. A method of preparing a veterinary layer bolus according to claim 1 having a sustained release layer contiguous with an immediate release layer which comprises preparing separate immediate and sustained release granulations containing a medicament and a filler which at least in the sustained release granulation is of such a density that the bolus will lodge in the rumeno-reticular sac of the ruminant animal, placing said granulations in separate hoppers and selectively compressing said granulations into a layered bolus.

6. A method according to claim 5 wherein the medicament is a sulfonamide or antibiotic and the dense filler is calcium sulphate dihydrate or iron powder.

7. A method according to claim 6 wherein the medicament is sulfamethazine and the filler matrix is calcium sulfate dihydrate.

8. A method of treating scours in calves wherein a bolus according to claim 3 is administered orally to the calves.

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Agent for the Applicants.

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1330829 COMPLETE SPECIFICATION
1 SHEET This drawing is a reproduction of the Original on a reduced scale

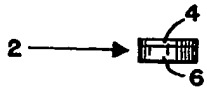

FIG. 1. (PRIOR ART)

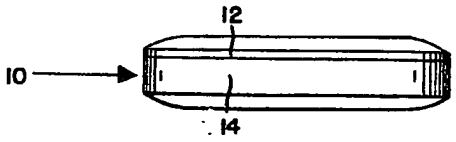

FIG. 2.
(PRESENT INVENTION)

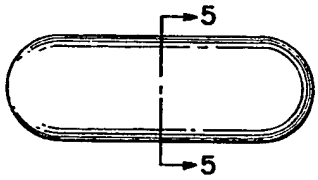

FIG. 3.

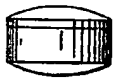

FIG. 4.

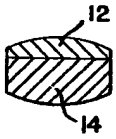

FIG. 5.